SPECIFICATION AMENDMENTS

Please replace the first paragraph on page 1 with the following rewritten paragraph:

[01] This application claims priority under 35 U.S.C. § 119(e) to Serial ~~No. 60/_____, (Atty. docket 511583000200)~~ No. 60/308,655 filed 27 July 2001. The contents of this application are incorporated herein by reference.

CLAIMS AMENDMENT

1. (currently amended): A method to isolate and characterize a membrane-bound receptor along with its microenvironment which method comprises

providing a solid support coupled to a ligand which specifically binds said receptor;

treating said solid support with a sample comprising nucleated cells or organelles thereof comprising said membrane-bound receptors, and which cells or organelles have not been surface-treated,

wherein a complex is formed between said membrane-bound receptor and the ligand thus generating a ligand/receptor complex comprising the receptor and its microenvironment, which complex is coupled to solid support through the ligand thus providing a complexed solid support;

separating the complexed solid support from the remainder of the sample;

subjecting the separated complexed solid support to a force sufficient to dissociate the receptor and its microenvironment from the membrane but insufficient to disrupt the ligand/receptor complex;

thus obtaining complexed solid support coupled to a ligand/receptor complex whereby the receptor retains its microenvironment but is separated from the membrane~~, and~~

~~analyzing the microenvironment of the receptor~~

removing the ligand/receptor complex comprising the receptor and its microenvironment from the complexed solid support, and

analyzing the microenvironment of the receptor.

2-3. (canceled)

4. (original): The method of claim 1 wherein the cells are vertebrate cells.

5. (original): The method of claim 4 wherein the cells are tumor cells or diseased cells.

6. (currently amended): The method of ~~claim 3~~ claim 1 wherein the cells are hematopoietic cells, or cells from adipose, areolar, connective, elastic, epithelial, endothelial, neural, mucous or reticular tissues.

7. (original): The method of claim 1 wherein the ligand is an antibody or an immunospecific portion thereof.

8. (original): The method of claim 1 wherein the receptor comprises an HLA antigen.

9. (original): The method of claim 1 wherein the receptor comprises a tumor associated antigen.

10. (original): The method of claim 1 wherein the receptor is a cytokine receptor, a hormone receptor, an opioid receptor, or a steroid receptor.

11. (original): The method of claim 1 wherein the force is achieved through extrusion.

12. (original): The method of claim 1 wherein the force is achieved through vortexing or shaking.

13. (original): The method of claim 1 wherein the force is achieved through sonication.

14. (original): The method of claim 1 wherein the solid support comprises beads.

15. (original): The method of claim 14 wherein said beads are polyacrylamide beads, polystyrene beads, Sephadex beads, or latex beads.

16. (original): The method of claim 1 wherein the solid support is a multi-well plate.

17. (currently amended): The method of ~~claim 2~~ claim 1 wherein the ligand is coupled to the solid support through a linker containing a photocleavable portion and said removing is effected by exposing the linker to light.

18. (currently amended): The method of ~~claim 2~~ claim 1 wherein the ligand is coupled to solid support through a linker containing a portion cleavable by an enzyme and said removing is effected by exposing said linker to said enzyme.

19. (canceled)

20. (currently amended): A method to recover a multiplicity of receptors along with their microenvironments which method comprises:

providing a multiplicity of solid support portions each coupled to a different ligand;

treating ~~a sample comprising nucleated cells that comprise at least two cell surface receptors, wherein said cells are not surface treated with~~ said multiplicity of solid support portions with a sample comprising nucleated cells that comprise at least two cell surface receptors, wherein said cells are not surface treated under conditions wherein ligand/receptor complexes are formed between said ligands and receptors at said cell surfaces which complexes are coupled to said solid support portions through the ligands, thus providing complexed solid support portions;

removing the complexed solid support portions from the sample; and

subjecting the complexed solid support portions to forces sufficient to remove the receptors and their microenvironments from the surface of said cells but insufficient to disrupt the ligand/receptor complexes,

removing the ligand/receptor complexes comprising the receptors and their microenvironments from the complexed solid support portions, and

analyzing the respective microenvironments of at least two receptors.

21. (canceled)

22. (original): The method of claim 20 which further includes identifying the receptors.

23. (canceled)

24. (original): The method of claim 22 which further includes organizing the identified receptors into a profile characteristic of the membrane sample.

25-26. (canceled)

27. (currently amended): The method of ~~claim 26~~ claim 20 wherein said ligands are monoclonal antibodies.

28. (new): The method of claim 20 wherein the ligands are coupled to the solid support portions through linkers each containing a photocleavable site and said removing is effected by exposing the linkers to light.

29. (new): The method of claim 20 wherein the ligands are coupled to solid support portions through linkers each containing a site cleavable by an enzyme and said removing is effected by exposing said linkers to said enzyme.

30. (new): The method of claim 20 wherein the cells are vertebrate cells.

31. (new): The method of claim 30 wherein the cells are tumor cells or diseased cells.

REMARKS

Formal Matters and Amendments

Applicant notes the requirement for a new oath identifying the provisional application from which priority is claimed. A new oath in compliance with this request is enclosed. Similarly, the specification has been amended to insert the serial number of the provisional application, which is now available. Claim 26, objected to under 35 U.S.C. § 1.75(c) has been canceled.

With regard to amendments to the claims, claim 1 has been amended to clarify that the treated solid support is "complexed" and that succeeding steps involve the complexed solid support. The limitations of claim 2 have been inserted into claim 1 to expedite prosecution. Claims 3 and 19 have also been canceled to expedite prosecution and the dependencies of claims 6, 17 and 18 corrected.

Claim 20 has been reworded as kindly suggested by the Examiner and the limitations of claim 21 have been inserted into this claim, again to expedite prosecution. Claims 23 and 25 have been canceled as dependent on a canceled claim; claim 26 has been canceled as redundant and claim 27 has been amended to depend from claim 20. Applicant has added new claims 28-29 which parallel claims 17 and 18; these simply add the limitations of means of coupling the linker to solid support to the situation of multiple portions. Similarly, claims 30 and 31 apply the limitations of claims 4 and 5 to claim 20.

No new matter has been added and entry of the amendment is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

These rejections have been obviated by amendment; claims 19 and 26 have been canceled and claim 20 has been amended for clarification as suggested.

The Art Rejections

Claims 1-4, 6-7, 10-12, 14-15, 18-23 and 26 were rejected as assertedly obvious over Jakobovits, *et al.,* in combination with Edelman, *et al.* (*Methods in Enzymology*) and as necessary Edelman, *et al.* (3,843,324). Applicant appreciates the recognition that the claimed methods differ from those described in the primary Jakobovits document. Respectfully, however, it is not believed that Edelman resolves these deficiencies, nor is it believed that there is any motivation to combine the teachings of Jakobovits with those of Edelman. Perhaps some confusion has been introduced through the coincidental use of the term "plucking" on page 199 of Edelman in a different context from which the term "plucking" is used in the present application.

Edelman, unlike Jakobovits and unlike the claimed invention, is directed to a method to separate cells by binding the entire cells to fibers through interaction with ligands and then releasing the cells. There is no description in Edelman of the essential feature of the invention which is to remove a membrane-bound receptor and its microenvironment from the cell itself. Thus, Edelman and Jakobovits are related to two entirely different enterprises – Jakobovits (and the present invention) succeed in removing receptors and their microenvironments from cells and Edelman merely describes separating cells from one another based on their surface markers. Thus, Edelman, *et al.,* do not teach that the methods of Jakobovits can be applied to nucleated or non-surface treated cells or that Jakobovits' methods may be employed using anything other than lectin as a ligand. And although Jakobovits refers in its closing paragraph to the possibility of employing these techniques to lymphocytes, no description of the actual application to lymphocytes is present so as to enable such a practice, nor is anything other than lectin/receptor interaction contemplated.

To expedite prosecution, applicant has inserted the limitations of claim 2 into claim 1 and of claim 21 into claim 20. These claims require that the ligand/receptor complex that comprises the receptor and its microenvironment be removed from the complexed solid support. None of the methods described by either Jakobovits or Edelman would succeed in achieving this, nor is there any suggestion in any document that the complex be removed along with its ligand. The Office points to page 1485 (conclusion of the last paragraph) of Jakobovits, but it should be noted that both of the methods for removal described would result in retaining the ligand on the solid support. The first method is to supply a competing sugar so as to compete for the ligand which remains on the solid support. The second method is by boiling, which would not disrupt the covalent bond attaching the lectin to the solid support (the solid support being CNBr activated Sepharose beads). Thus, Jakobovits does not suggest removing the receptor and its microenvironment along with the ligand from the solid support.

Thus, even if the combination of Jakobovits with Edelman were properly made, the combination does not teach or suggest the invention as now claimed. The motivation provided by the Office for combining Jakobovits with Edelman is, in any event, respectfully disputed by applicant. The Office does recognize that Edelman is concerned with isolating cell populations, not with isolating receptors from their microenvironments. The Office, however, points to page 195 of Edelman as teaching that the method may be used for a "isolation of cell surface markers." However, Edelman does not appear to be suggesting the described method for isolating cell surface markers, but rather the use of Edelman's method for obtaining pure populations of cells, which cells, in turn can be used as substrates for isolating surface markers by an unspecified method.

The comments regarding pages 208-209 of Edelman do not appear to provide motivation for combining with Jakobovits; Edelman is suggesting that there may be some damage to the cells which is avoidable when they are removed from the fibers; there is no suggestion in Edelman of achieving the goal of the present invention (or of Jakobovits) of isolating a receptor along with the immediate microenvironment specifically associated with the receptor. Rather, Edelman simply suggests that the cell membrane may be damaged in some unspecified way, having nothing to do with the microenvironment of the receptor.

Thus, the combination of Edelman and Jakobovits both fails to teach the invention as now claimed and is not motivated either by the teachings contained in either document or by a commonality of the problem to be solved, or by the high profile of one of the documents (the three factors outlined by the Court as acceptable bases for combination in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998)).

Similar comments as the foregoing are applicable to the rejection of claim 20 and its dependent claims. There is no teaching in any document of the further limitations inserted into claim 20 by amendment so that the combination of Jakobovits and Edelman fails to teach the invention as now claimed; further, there is no motivation to combine these teachings for the reasons outlined above.

With respect to claim 18 which was included in this rejection, applicant notes that although this claim requires that the ligand be coupled to solid support through a linker containing a portion cleavable by an enzyme, and Edelman is cited presumably as disclosing such a feature at the paragraph that spans pages 198-199, there is no mention of an enzyme cleavable linker in Edelman at this location (or elsewhere that applicant is able to find).

In light of the foregoing discussion, it is believed that claims 1 and 20 and their dependent claims are patentable over the cited art. Therefore, the rejection of claims 8, 16, 24-25 and 27 on the same basis, but with the addition of Chang, and of claim 9 on the same basis with the addition of Kupchik and claim 13 with the addition of Seifert are overcome as well. Respectfully, it is believed, further, that absent the invention, there is no suggestion to combine the teachings of Chang, Kupchik, or Seifert with the primary and secondary documents. None of the factors set fourth in *Rouffet* is present to motivate such combinations.

It is noted that no art rejection has been applied to claims 5 or 17 which are therefore, presumably, considered free of the art. As noted above, the citation with regard to claim 18 appears to be in error. Accordingly, it appears clear that at least claims 5, 17, 18, 28, 29 and 31 are free of any art rejection at all.

Rejections for Double-Patenting

The rejections for double-patenting (both statutory and obviousness-type) are requested to be held in abeyance until otherwise allowable claims are recognized. Prosecution has not begun in application 10/209,328, which is a continuation-in-part of the present application and the ultimate nature of the claims in the present application and those in the continuation-in-part are not as yet determined.

CONCLUSION

The claims have been amended to expedite prosecution by requiring that the ligand/receptor complex comprising the receptor and its microenvironment be removed as such from the complexed solid support. No document suggests either that this be done or any means for carrying it out. Further, the combination of Jakobovits and Edelman appears to lack the

required motivation. Claims 5, 17, 18, 28, 29 and 31 are clearly free of the cited art. Accordingly, it is believed that claims 1, 4-18, 20, 22, 24 and 27-29 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 511582006000.

Respectfully submitted,

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